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L3: Entry 12 of 161 File: PGPB Feb 12, 2004

DOCUMENT-IDENTIFIER: US 20040029278 A1
TITLE: Eukaryotic layered vector initiation systems

Detail Description Paragraph:
[0806] Other viral vectors, such as those derived from unrelated vectors (e.g., RSV, MMT V or HIV), also may be used in the same manner to generate packaged vectors from primary cells. In one embodiment, these adenoviral vectors are used in conjunction with primary cells, giving rise to recombinant alphavirus particles.

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L3: Entry 89 of 161 File: USPT Nov 25, 2003

DOCUMENT-IDENTIFIER: US 6653101 B1
** See image for Certificate of Correction **
TITLE: Recombinant DNA method and host cells

Other Reference Publication (2):
Brad Zerler et al. Adenovirus E1A Coding Sequences That Enable ras and pmt Oncogenes To Transform Cultured Primary Cells, Molecular And Cellular Biology, Mar. 1986, p. 887-899, vol. 6, No. 3.*

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L3: Entry 147 of 161 File: USPT Sep 23, 1997

DOCUMENT-IDENTIFIER: US 5670347 A
TITLE: Peptide-mediated gene transfer

Brief Summary Text (10):
Other viruses have been used to generate recombinant viral vectors for gene transfer studies. Adenovirus, adeno-associated virus, herpes simplex virus, and even HIV have been employed as vectors to introduce genes into both established cell lines and primary cells. Some of these viral vectors are capable of transferring genes into non-dividing cells. R. J. Samulski, et al., EMBO J. 10: 3941 (1981); J. D. Tratschin, et al., Mol. Cell. Biol. 5: 3251 (1985); P. L. Hermonat, et al., Proc. Nat'l Acad. Sci. (USA) 81: 6466 (1984); D. J. Fink, et al., Human Gene Therapy 3: 11 (1992).

Detailed Description Text (25):
In order to extend the life of primary cells that are endogenously incapable of extended growth in vitro, the cells are transfected with different oncogenes, such as SV40 large T antigen, polyoma large T antigen, adenovirus E1A and E1B, v-fms, Bc12, myc and ras. The oncogenes can be used either alone, in pairs of various combinations, or in combinations of more than two oncogenes.

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L3: Entry 154 of 161 File: USPT Nov 16, 1993

DOCUMENT-IDENTIFIER: US 5262359 A
TITLE: Method of propagating human paramyxoviruses using continuous cell lines

Brief Summary Text (6):
(c) Primary cell lines derived from the kidneys of rhesus monkeys, are sometimes latently infected with adenoviruses, enteroviruses, and herpesviruses, and almost always are infected with SV-5 (a myxovirus) and SV-40 (a papovavirus). Although these agents are not known to infect man, they often compromise virus isolation and identification, reagent production, and vaccine testing, thus constituting a major contamination problem in the laboratory;

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L7: Entry 30 of 92 File: PGPB Jan 2, 2003

DOCUMENT-IDENTIFIER: US 20030003566 A1
TITLE: Cell line preparing and producing ovine adenovirus vectors

Abstract Paragraph:
The invention relates to the ovine embryo cell line HVO-156 (DSM ACC2440), or to cell lines derived therefrom, and to their use for preparing and propagating ovine adenoviruses, in particular recombinant ovine adenoviruses which are derived from the isolate OAV 287.

Summary of Invention Paragraph:
[0001] The invention relates to the ovine embryo cell line HVO-156 (DSM ACC2440), or to cell lines derived therefrom, and to their use for preparing and propagating ovine adenoviruses, in particular recombinant ovine adenoviruses which are derived from the isolate OAV 287.

Summary of Invention Paragraph:
[0005] There therefore exists a need to provide alternative cell lines which have a higher efficiency for preparing adenoviruses. It has been found that ovine embryo cell lines, in particular the ovine embryo cell line HVO-156 (DSM ACC2440), or cell lines derived therefrom, enable adenoviruses to be propagated with such a degree of efficiency. These cells are distinguished by a long life span (the ability to be passaged at least 40 times, corresponding to >100 generations), the ability to be readily transfected with recombinant DNA, a high degree of efficiency in the formation of recombinant ovine adenoviruses and a high rate of propagation of recombinant ovine adenoviruses.

Summary of Invention Paragraph:
[0007] The deposited cell line, or cell lines which are derived therefrom, for example by subcloning, and also other ovine embryo cell lines, are suitable for preparing and/or propagating adenoviruses, in particular ovine adenoviruses, such as ovine adenoviruses of the isolate OAV 287 and recombinant viruses which are derived therefrom.

CLAIMS:

1. The use of ovine embryo cell lines for preparing or/and propagating adenoviruses.

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L7: Entry 58 of 92 File: USPT Apr 30, 2002

DOCUMENT-IDENTIFIER: US 6379944 B1
** See image for Certificate of Correction **
TITLE: Mammalian cell lines expressing bovine adenovirus functions

Other Reference Publication (87):
Jones, N. and Shenk, T. (1979). "Isolation of adenovirus type 5 host range deletion mutants defective for transformation of rat embryo cells," Cell 17(3):683-689.

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L7: Entry 69 of 92 File: USPT Feb 6, 2001

DOCUMENT-IDENTIFIER: US 6184032 B1
TITLE: Identification of genes encoding cell surface antigens using CREF-Trans 6 cells

Detailed Description Text (72):
Generation of Monoclonal Antibodies. The procedures we have utilized to generate MoAbs are similar to those described previously for generating MoAbs toward human TAAs tumor associated antigenst (50), HLA antigens (51), type 5 adenovirus-transformed Sprague-Dawley rat embryo cells (52), X-ray-transformed C3H-10T 1/2 cells (53) and NIH-3T3 transfectants containing and expressing the neuro/glioblastoma (neu) oncogene (39). Spleen cells prepared from immunized mice were hybridized with the non-secreting myeloma cells NSI in the presence of polyethyleneglycol (PEG) according to the procedure of Kohler and Milstein (54) with minor modifications. Twenty-four hours after fusion the hybrid clones were replated in 96 well plates in HAT medium to select for hybrid cells.

L7: Entry 80 of 92 File: USPT Dec 22, 1998

DOCUMENT-IDENTIFIER: US 5851764 A
TITLE: Human prostate tumor inducing gene-1 and uses thereof

Detailed Description Text (127):
12. Fisher, P. B., Babiss, L. E., Weinstein, I. B., et al. (1982) Analysis of type 5 adenovirus transformation with a cloned rat embryo cell line (CREF), Proc. Natl. Acad. Sci., USA, 79:3527-3531.

Detailed Description Text (135):
20. Duigou, G. J., Su, Z-z., Babiss, L. E., et al. (1991) Analysis of viral and cellular gene expression during progression and suppression of the transformed phenotype in type 5 adenovirus-transformed rat embryo cells, Oncogene, 6:1813-1824.

L7: Entry 86 of 92 File: USPT Jan 24, 1978

DOCUMENT-IDENTIFIER: US 4070453 A
TITLE: Diploid porcine embryonic cell strains, cultures produced therefrom, and use of said cultures for production of vaccines

Detailed Description Text (29):
Yet other eleventh passage diploid porcine embryonic strain cells were subcultured into Leighton tubes containing coverslips. After appropriate incubation, these coverslips were assayed by the direct fluorescent antibody technique, using specific fluorochrome labeled antibodies, against: PI.sub.3 virus, infectious bovine rhinotracheitis (IBR) virus, BVD virus, BEV virus (four serotypes), BAV virus (two serotypes), bovine parvovirus (BPV), R virus, PPV virus, pseudorabies virus (PSV), HC virus, RV virus, porcine adenovirus (PAV) virus, and TGE virus. Examination of the coverslips infected with specific agents as positive test controls indicated the diploid porcine embryonic cell strain was capable, as established by positive fluorescence, of supporting the growth of the following viruses: TGE, PPV, PI.sub.3, R, RV, BEV, BAV and BPV.

L11: Entry 5 of 67 File: PGPB May 6, 2004

DOCUMENT-IDENTIFIER: US 20040087027 A1
TITLE: Recombinant adenoviral vector and methods of use

Brief Description of Drawings Paragraph:
[0016] FIG. 1 shows a recombinant adenoviral vector of this invention. This construct was assembled as shown in FIG. 1. The resultant virus bears a 5' deletion of adenoviral sequences extending from nucleotide 356 to 4020 and eliminates the E1a and E1b genes as well as the entire protein IX coding sequence, leaving the polyadenylation site shared by the E1b and pIX genes intact for use in terminating transcription of any desired gene.

Detail Description Paragraph:
[0036] Contrary to what has been known in the art, this invention claims the use of recombinant adenoviruses bearing deletions of the protein IX gene as a means of reducing the risk of wild-type adenovirus contamination in virus preparations for use in diagnostic and therapeutic applications such as gene therapy. As used herein, the term "recombinant" is intended to mean a progeny formed as the result of genetic engineering. These deletions can remove an additional 500 to 700 base pairs of DNA sequence that is present in conventional E1 deleted viruses (smaller, less desirable, deletions of portions of the pIX gene are possible and are included within the scope of this invention) and is available for recombination with the Ad5 sequences integrated in 293 cells. Recombinant adenoviruses based on any group C virus, serotype 1, 2, 5 and 6, are included in this invention. Also encompassed by this invention is a hybrid Ad2/Ad5 based recombinant virus expressing the human p53 cDNA from the adenovirus type 2 major late promoter. This construct was assembled as shown in FIG. 1. The resultant virus bears a 5' deletion of adenoviral sequences extending from about nucleotide 357 to 4020 and eliminates the E1a and E1b genes as well as the entire protein IX coding sequence, leaving the polyadenylation site shared by the E1b and protein IX genes intact for use in terminating transcription of any desired gene. A separate embodiment is shown in FIG. 4. Alternatively, the deletion can be extended an additional 30 to 40 base pairs without affecting the adjacent gene for protein IVa2, although in that case an exogenous polyadenylation signal is provided to terminate transcription of genes inserted into the recombinant virus. The initial virus constructed with this deletion is easily propagated in 293 cells with no evidence of wild-type viral contamination and directs robust p53 expression from the transcriptional unit inserted at the site of the deletion.

L11: Entry 5 of 67 File: PGPB May 6, 2004

DOCUMENT-IDENTIFIER: US 20040087027 A1
TITLE: Recombinant adenoviral vector and methods of use

Brief Description of Drawings Paragraph:
[0016] FIG. 1 shows a recombinant adenoviral vector of this invention. This construct was assembled as shown in FIG. 1. The resultant virus bears a 5' deletion of adenoviral sequences extending from nucleotide 356 to 4020 and eliminates the E1a and E1b genes as well as the entire protein IX coding sequence, leaving the polyadenylation site shared by the E1b and pIX genes intact for use in terminating transcription of any desired gene.

Detail Description Paragraph:
[0036] Contrary to what has been known in the art, this invention claims the use of recombinant adenoviruses bearing deletions of the protein IX gene as a means of reducing the risk of wild-type adenovirus contamination in virus preparations for use in diagnostic and therapeutic applications such as gene therapy. As used herein, the term "recombinant" is intended to mean a progeny formed as the result of genetic engineering. These deletions can remove an additional 500 to 700 base pairs of DNA sequence that is present in conventional E1 deleted viruses (smaller, less desirable, deletions of portions of the pIX gene are possible and are included within the scope of this invention) and is available for recombination with the Ad5 sequences integrated in 293 cells. Recombinant adenoviruses based on any group C virus, serotype 1, 2, 5 and 6, are included in this invention. Also encompassed by this invention is a hybrid Ad2/Ad5 based recombinant virus expressing the human p53 cDNA from the adenovirus type 2 major late promoter. This construct was assembled as shown in FIG. 1. The resultant virus bears a 5' deletion of adenoviral sequences extending from about nucleotide 357 to 4020 and eliminates the E1a and E1b genes as well as the entire protein IX coding sequence, leaving the polyadenylation site shared by the E1b and protein IX genes intact for use in terminating transcription of any desired gene. A separate embodiment is shown in FIG. 4. Alternatively, the deletion can be extended an additional 30 to 40 base pairs without affecting the adjacent gene for protein IVa2, although in that case an exogenous polyadenylation signal is provided to terminate transcription of genes inserted into the recombinant virus. The initial virus constructed with this deletion is easily propagated in 293 cells with no evidence of wild-type viral contamination and directs robust p53 expression from the transcriptional unit inserted at the site of the deletion.

L11: Entry 42 of 67 File: USPT Feb 17, 2004

US-PAT-NO: 6692966
DOCUMENT-IDENTIFIER: US 6692966 B2

TITLE: Packaging systems for human recombinant adenovirus to be used in gene therapy

DATE-ISSUED: February 17, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Fallaux; Frits J.	Leiderdorp			NL
Hoeben; Robert C.	Leiden			NL
Bout; Abraham	Moerkapelle			NL
Valerio; Domenico	Oegstgeest			NL
van der Eb; Alex J.	Oegstgeest			NL

US-CL-CURRENT: 435/456; 424/93.2, 435/320.1, 435/325, 435/455

CLAIMS:

What is claimed is:

1. A method for producing a recombinant adenovirus comprising a gene of interest, said method not producing an adenovirus having a functional E1 region, said method comprising: providing a complementing cell, said complementing cell harboring a first nucleic acid comprising adenoviral nucleic acid encoding functional E1A protein and E1B protein but not pIX protein; transferring recombinant nucleic acid into said complementing cell, said recombinant nucleic acid comprising: a second nucleic acid containing adenoviral nucleic acid including at least one encapsidation signal, and functional Inverted Terminal Repeats at or near both termini, said second nucleic acid further comprising a gene of interest and all sequences required for replication of said second nucleic acid which are not provided by said complementing cell; said recombinant nucleic acid lacking overlapping sequences with the first nucleic acid, which overlap could otherwise lead to homologous recombination resulting in the formation of adenovirus having a functional E1 region; culturing said complementing cell; and harvesting the recombinant adenovirus produced from said complementing cell.

2. The method according to claim 1 wherein said recombinant nucleic acid is one nucleic acid molecule in linear form.

3. The method according to claim 1 wherein said complementing cell is derived from a primary cell.

4. The method according to claim 1 wherein said recombinant nucleic acid is DNA.

5. A method of producing, in a producer cell, recombinant adenovirus comprising a gene of interest, said method comprising: culturing a producer cell comprising a first nucleic acid sequence encoding at least adenoviral E1A region gene product but not encoding pIX protein and a second nucleic acid containing adenoviral nucleic acid including at least one encapsidation signal and functional Inverted Terminal Repeats at or near both termini, said second nucleic acid further comprising a gene of interest and all sequences required for replication of said second nucleic acid which are not provided by said producer cell, said second nucleic acid having no overlapping sequences with respect to said first nucleic acid sequence which overlap could otherwise lead to homologous recombination resulting in the formation of adenovirus having a functional E1 region; and harvesting recombinant adenovirus produced from said cell.

6. The method according to claim 5 wherein said producer cell further comprises a sequence encoding adenoviral E2A region gene product, wherein said sequence encoding adenoviral E2A region gene product is selected from the group consisting of a DNA sequence encoding the wild-type E2A region operably linked to an inducible promoter and a DNA sequence encoding a temperature sensitive 125 mutation.

7. The method according to claim 1, wherein said recombinant nucleic acid comprises at least two nucleic acid molecules that upon homologous recombination are capable of forming said second nucleic acid.

8. The method according to claim 1, wherein said first nucleic acid is integrated into the genome of said complementing cell.

9. The method according to claim 5, wherein said first nucleic acid sequence is integrated into the genome of said producer cell.

10. The method according to claim 5, wherein said first nucleic acid sequence further encodes an adenoviral E1B region gene product.

11. The method according to claim 6, wherein said sequence encoding adenoviral E2A region gene product is integrated into the genome of the producer cell.

12. The method according to claim 6, wherein the recombinant adenovirus produced has a deletion in the E2A region.

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L11: Entry 46 of 67 File: USPT Aug 5, 2003

US-PAT-NO: 6602706
DOCUMENT-IDENTIFIER: US 6602706 B1
** See image for Certificate of Correction **

TITLE: Packaging systems for human recombinant adenovirus to be used in gene therapy

DATE-ISSUED: August 5, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Fallaux; Frits Jacobus	Leiderdorp			NL
Hoeben; Robert Cornelis	Leiden			NL
Van Der Eb; Alex Jan	Oegstgeest			NL
Bout; Abraham	Moerkapelle			NL
Valerio; Domenico	Leiden			NL

US-CL-CURRENT: 435/325; 435/320.1, 435/455, 435/69.1, 435/91.4

CLAIMS:

What is claimed is:

1. An established adenovirus packaging cell comprising a first nucleic acid sequence consisting of a nucleic acid sequence encoding an adenoviral E1A region gene product and a constitutive promoter controlling said nucleic acid sequence encoding said adenoviral E1 A region gene product, said established adenovirus packaging cell further comprising: one or more recombinant nucleic acid molecules lacking overlapping sequences with the first nucleic acid sequence of said established adenovirus packaging cell, the overlapping sequences otherwise enabling homologous recombination leading to replication competent virus in said established adenovirus packaging cell.

2. The established adenovirus packaging cell of claim 1, wherein said established adenovirus packaging cell does not express E1B products.

3. The established adenovirus packaging cell of claim 1, wherein the genetic information encoding E1B products is absent.

4. The established adenoviris packaging cell of claim 1, further comprising a marker gene.

5. The established adenovirus packaging cell of claim 4, wherein said marker gene is under control of an E1 B responsive promoter.

6. The established adenovirus packaging cell of claim 1, wherein said established adenovirus packaging cell does not express a 21 kDa E1B product.

7. The established adenovirus packaging cell of claim 1, wherein genetic information encoding a 21 kDa E1B product is not present.

8. The established adenovirus packaging cell of claim 1, wherein said established adenovirus packaging cell is a diploid cell.

9. The established adenovirus packaging cell of claim 1, wherein said established adenovirus packaging cell is of non-human origin.

10. The established adenovirus packaging cell of claim 1, wherein said established adenovirus packaging cell is of monkey origin.

11. An established adenovirus packaging cell comprising a first nucleic acid sequence consisting of a nucleic acid sequence encoding an adenoviral E1A region gene product and said established adenovirus packaging cell further comprising a nucleic acid sequence encoding an adenoviral E2A region gene product under the control of an inducible promoter, said established adenovirus packaging cell further comprising: one or more recombinant nucleic acid molecules lacking overlapping sequences with the first nucleic acid sequence of said established adenovirus packaging cell, the overlapping sequences otherwise enabling homologous recombination leading to replication competent virus in said established adenovirus packaging cell.

12. The established adenovirus packaging cell of claim 11, wherein the nucleic acid sequence encoding the adenoviral E2A region gene product is mutated to alter the host range of the adenovirus as compared to wild-type adenovirus.

13. The established adenovirus packaging cell of claim 11, wherein said established adenovirus packaging cell does not express E1B products.

14. The established adenovirus packaging cell of claim 11, wherein the genetic information encoding E1B products is absent.

15. The established adenovirus packaging cell of claim 11, wherein said established adenovirus packaging cell does not express a 21 kDa E1B product.

16. The established adenovirus packaging cell of claim 11, wherein genetic information encoding a 21 kDa E1B product is not present.

17. The established adenovirus packaging cell of claim 11, wherein said established adenovirus packaging cell is a diploid cell.

18. The established adenovirus packaging cell of claim 11, wherein said established adenovirus packaging cell is of non-human origin.

19. The established adenovirus packaging cell of claim 18, wherein said established adenovirus packaging cell is of monkey origin.

20. An established adenovirus packaging cell comprising a first nucleic acid sequence consisting of a nucleic acid sequence encoding an adenoviral E1A region gene product and said established adenovirus packaging cell further comprising a nucleic acid sequence encoding an adenoviral E2A region gene product having a ts125 mutation, said established adenovirus packaging cell further comprising: one or more recombinant nucleic acid molecules lacking overlapping sequences with the first nucleic acid sequence, the overlapping

sequences otherwise enabling homologous recombination leading to replication competent virus in said established adenovirus packaging cell.

21. The established adenovirus packaging cell of claim 20, wherein said established adenovirus packaging cell does not express E1B products.

22. The established adenovirus packaging cell of claim 20, wherein the genetic information encoding E1B products is absent.

23. The established adenovirus packaging cell of claim 20, wherein said established adenovirus packaging cell does not express a 21 kDa E1B product.

24. The established adenovirus packaging cell of claim 20, wherein genetic information encoding a 21 kDa E1B product is not present.

25. The established adenovirus packaging cell of claim 20, wherein said established adenovirus packaging cell is a diploid cell.

26. The established adenovirus packaging cell of claim 20, wherein said established adenovirus packaging cell is of non-human origin.

27. The established adenovirus packaging cell of claim 26, wherein said established adenovirus packaging cell is of monkey origin.

28. The established adenovirus packaging cell of claim 20, wherein the nucleic acid sequence encoding the adenoviral E2A region gene product is mutated to alter the host range of the adenovirus as compared to wild-type adenovirus.

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L11: Entry 58 of 67 File: USPT Jul 24, 2001

US-PAT-NO: 6265212
DOCUMENT-IDENTIFIER: US 6265212 B1

TITLE: Packaging systems for human recombinant adenovirus to be used in gene therapy

DATE-ISSUED: July 24, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Fallaux; Frits J.	Leiderdorp			NL
Hoeben; Robert C.	Leiden			NL
Bout; Abraham	Moerkapelle			NL
Valerio; Domenico	Leiden			NL
van der Eb; Alex J.	Oegstgeest			NL
Schouten; Govert	Leiden			NL

US-CL-CURRENT: 435/320.1; 424/93.21, 435/235.1, 435/325, 435/69.1, 536/23.1

CLAIMS:

What is claimed is:

1. A method of making replication-defective adenovirus lacking functional adenoviral E1A and E1B proteins comprising a) providing a primary cell comprising a first nucleic acid sequence encoding functional E1A protein and E1B protein but not pIX protein; b) transfecting said cell with a second nucleic acid sequence comprising at least one functional adenoviral encapsidating signal and at least one functional adenoviral inverted terminal repeat, wherein said second nucleic acid sequence does not encode functional adenoviral E1A or E1B; and further wherein said first and second nucleic acids sequences lack overlapping sequences, the overlapping sequences otherwise enabling homologous recombination leading to replication competent adenovirus in said cell; c) culturing the transfected cell; and d) harvesting replication-defective adenovirus lacking functional adenoviral E1A and E1B from the cultured cell.

2. The method according to claim 1, wherein said second nucleic acid sequence is in linear form and comprises functional Inverted Terminal Repeats at or near both termini.

3. The method according to claim 1, wherein said second nucleic acid sequence is DNA.

4. The method according to claim 1, wherein the first or second nucleic acid sequence comprises a mutation in the E2A adenoviral gene that encodes a temperature sensitive gene product.

5. The method of claim 1, wherein the primary cell is of human origin.

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L11: Entry 61 of 67 File: USPT Oct 17, 2000

DOCUMENT-IDENTIFIER: US 6133028 A
TITLE: Defective adenoviruses and corresponding complementation lines

CLAIMS:

14. The complementation line of claim 1 wherein said complementation element comprises a fragment of an adenoviral genome lacking the 5'ITR, the encapsidation region, the promoter of the E1A region and the transcription termination signal of E1B and pIX transcription units.

30. The complementation line of claim 19 wherein said complementation element comprises a fragment of an adenoviral genome lacking the 5'ITR, the encapsidation region, the promoter of the E1A region and the transcription termination signal of E1B and pIX transcription units.

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L11: Entry 64 of 67 File: USPT Mar 7, 2000

US-PAT-NO: 6033908
DOCUMENT-IDENTIFIER: US 6033908 A
**** See image for Certificate of Correction ****

TITLE: Packaging systems for human recombinant adenovirus to be used in gene therapy

DATE-ISSUED: March 7, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Bout; Abraham	Ar Moerkapelle			NL
Hoeben; Robert Cornelis	Ex Leiden			NL

US-CL-CURRENT: 435/325; 424/93.21, 435/320.1, 435/455, 435/69.1, 514/44, 536/23.1

CLAIMS:

We claim:

1. A packaging cell deposited under No. 96022940 at the European Collection of Animal Cell Cultures at the Center for Applied Microbiology and Research.

2. The packaging cell according to claim 1, further comprising a packaging construct comprising an E1A-independent transcriptional initiation region operatively linked to an adenovirus E2A region.

3. The packaging cell according to claim 1, further comprising a recombinant expression vector IG.Ad.MLPI.TK shown in FIG. 12.

4. The packaging cell according to claim 1, further comprising a packaging construct comprising a mutation in an adenovirus E2A region such that at least one E2A gene product is temperature sensitive.

5. The packaging cell according to claim 1, further comprising a packaging construct comprising an E1A-independent transcriptional initiation region operatively linked to an adenovirus E2A region and a marker gene.

6. The packaging cell according to claim 1, further comprising a recombinant expression vector from a human adenovirus 5 genome from which nucleotides 459-3510 have been deleted.

7. The packaging cell according to claim 1, further comprising a packaging construct comprising a transcriptional initiation region operatively linked to an adenovirus ts125 E2A region.

8. A method of producing replication competent adenovirus-free adenoviral

vectors in a packaging cell, said method comprising:

growing a packaging cell according to claim 1, wherein said packaging cell or an ancestor of said packaging cell has been inoculated with a recombinant expression vector derived from a human adenovirus 5 genome from which nucleotides 459-3510 have been deleted, wherein said packaging cell has no adenoviral sequences which overlap with said recombinant expression vector that would lead to production of replication competent adenovirus whereby replication competent adenovirus-free adenoviral vectors are produced.

9. The method according to claim 8, wherein said recombinant expression vector is IG.Ad.MLPI.TK shown in FIG. 12.

10. A preparation of adeoviral particles free of replication competent adenovirus, produced according to the method of claim 8.

11. A mammalian cell comprising:

a packaging construct comprising nucleotides 459-3510 of a human adenovirus 5 genome, wherein said packaging construct lacks a pIX gene, and a recombinant expression vector derived from a human adenovirus genome and containing a pIX gene, wherein said packaging construct has no sequence overlap with said recombinant expression vector, and wherein said cell expresses E1A and E1B proteins encoded by said packaging construct and pIX is expressed from said recombinant expression vector.

12. The mammalian cell according to claim 11, wherein said packaging construct is pIG.E1A.E1B as shown in FIG. 4.

13. The mammalian cell according to claim 11 or 12, wherein said recombinant expression vector is IG.Ad.MLPI.TK as shown in FIG. 12.

14. A mammalian cell containing a packaging construct comprising:

nucleotides 459-3510 of a human adenovirus 5 genome, wherein said packaging construct lacks a pIX gene.

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L11: Entry 65 of 67 File: USPT Nov 30, 1999

US-PAT-NO: 5994128
DOCUMENT-IDENTIFIER: US 5994128 A
**** See image for Certificate of Correction ****

TITLE: Packaging systems for human recombinant adenovirus to be used in gene therapy

DATE-ISSUED: November 30, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Fallaux; Frits Jacobus	Be Leiderdorp			NL
Hoeben; Robert Cornelis	Ex Leiden			NL
Van der Eb; Alex Jan	Tw Oegstgeest			NL
Bout; Abraham	Ar Moerkapelle			NL
Valerio; Domenico	Ez Leiden			NL

US-CL-CURRENT: 435/325; 424/93.21, 435/320.1, 435/455, 435/69.1, 536/23.1

CLAIMS:

We claim:

1. A system for producing adenovirus incapable of replicating, said system comprising:

a primary cell containing a nucleic acid encoding adenoviral E1A and E1B gene products, wherein aid nucleic acid lacks a gene coding for active or functional pIX; and an isolated recombinant nucleic acid molecule for transfer into said primary cell, said isolated recombinant nucleic acid molecule based on or derived from an adenovirus of the family Adenoviridae, and further having

at least a functional encapsidating signal, and

at least one functional Inverted Terminal Repeat,

said isolated recombinant nucleic acid molecule lacking overlapping sequences with the nucleic acid of the cell, the overlapping sequences otherwise enabling homologous recombination leading to replication competent adenovirus in said primary cell into which said isolated recombinant nucleic acid molecule is to be transferred.

2. The system of claim 1 wherein said isolated recombinant nucleic acid molecule is in a linear form and comprises functional Inverted Terminal Repeats at or near both termini.

3. The system of claim 1 wherein said isolated recombinant nucleic acid molecule comprises a nucleic acid which alters the range of said adenovirus as compared to a wild-type adenovirus and wherein said primary cell is a non-human primary cell.

4. An adenoviral producer cell that does not produce replication competent adenovirus, said adenoviral producer cell comprising:

one or more recombinant nucleic acid molecules having no overlapping sequences with respect to one another which would otherwise allow for homologous recombination leading to replication competent adenovirus in said adenoviral producer cell, and wherein said adenoviral producer cell comprises a nucleic acid encoding adenoviral E1A and E1B gene products, said nucleic acid lacking a gene coding for functional or active pIX.

5. An adenoviral producer cell that does not produce replication competent adenovirus, said adenoviral producer cell comprising:

one or more recombinant nucleic acid molecules having no overlapping sequences with respect to one another which would otherwise allow for homologous recombination leading to replication competent adenovirus in said adenoviral producer cell, and wherein said adenoviral producer cell comprises a nucleic acid encoding adenoviral E1 and E1B gene products, said nucleic acid lacking a gene coding for functional or active pIX, and E2A gene product under the control of an inducible promoter.

6. An adenoviral producer cell that does not produce replication competent adenovirus, said adenoviral producer cell comprising:

one or more recombinant nucleic acid molecules having no overlapping sequences with respect to one another which would otherwise allow for homologous recombination leading to replication competent adenovirus in said adenoviral producer cell, said adenoviral producer cell comprises a nucleic acid encoding adenoviral E1 and E2A gene products, said nucleic acid lacking a gene coding for functional or active pIX, and wherein said E2A gene product encodes a temperature sensitive mutation.

7. The producer cell according to claim 4, wherein any one or more of said recombinant nucleic acid molecules thereof further comprises a marker gene.

8. The producer cell according to claim 7, wherein the marker gene is under control of an E1A adenoviral gene product responsive promoter.

9. The producer cell according to claim 4 or 5, which is a diploid cell.

10. The producer cell according to claim 4 or 5, which is of non-human origin.

11. The producer cell according to claim 3 which is of monkey origin.

12. The system of claim 3 wherein said isolated recombinant nucleic acid molecule is DNA.

13. The adenoviral producer cell of claim 4 or 5 wherein at least one of said one or more recombinant nucleic acid molecules comprises at least one functional encapsidating signal and one functional Inverted Terminal Repeat,

but lacks nucleotides 459-3510 of the E1 gene of adenovirus.

14. The adenoviral producer cell of claim 4 or 5 wherein at least one of said one or more recombinant nucleic acid molecules comprises at least one functional encapsidating signal and one functional Inverted Terminal Repeat, but lacks nucleotides 459-1713 of the E1 gene of adenovirus.

15. The producer cell according to claim 4 wherein a recombinant nucleic acid molecule thereof further comprises a mutated E2A adenoviral gene that encodes a temperature sensitive gene product.

16. An established adenoviral producer cell that lacks a gene encoding for active or functional pIX and does not produce replication competent adenovirus, said established adenoviral producer cell derived from a primary cell, said established adenoviral producer cell comprising:

one or more recombinant nucleic acid molecules having no overlapping sequences within each of the recombinant nucleic acid molecules, wherein said adenoviral producer cell comprises DNA sequences encoding functional adenoviral E1A and E1B gene products.

17. The established adenoviral producer cell of claim 16 wherein at least one of said one or more recombinant nucleic acid molecules further comprises DNA sequences encoding an adenoviral E2A gene product.

18. The established adenoviral producer cell of claim 16 wherein said DNA sequence encoding an adenoviral E2A gene product is selected from the group consisting of a DNA sequence encoding the wild-type E2A gene operably linked to an inducible promoter and a DNA sequence encoding a temperature sensitive 125 mutation.

19. The producer cell of claim 6 wherein said E2A gene product is under the control of an inducible promoter.

20. The system of claim 1 wherein said primary cell comprises a nucleic acid encoding a mutated E2 gene product which alters the host range of said adenovirus as compared to a wild-type adenovirus.

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L12: Entry 18 of 65 File: PGPB Jul 25, 2002

DOCUMENT-IDENTIFIER: US 20020098571 A1
TITLE: Rapid generation of recombinant adenoviral vectors

Summary of Invention Paragraph:
[0006] Most adenovirus vectors are based on the adenovirus type 5 (Ad5) backbone in which an expression cassette containing the foreign gene has been introduced in place of the early region 1 (E1) or early region 3 (E3). Viruses in which E1 has been deleted are defective for replication and are propagated in human complementation cells (e.g., 293 or 911 cells), which supply the missing gene products provide the E1 and pIX products in trans.

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L12: Entry 19 of 65 File: PGPB Jul 25, 2002

DOCUMENT-IDENTIFIER: US 20020098165 A1
TITLE: RECOMBINANT ADENOVIRUSES CONTAINING AN INDUCIBLE PROMOTER CONTROLLING A GENE OF VIRAL ORIGIN

Summary of Invention Paragraph:
[0007] In the particular case of recombinant adenoviruses, the constructions described in the prior art are generally adenoviruses from which the E1 (E1a and/or E1b) and possibly E3 regions have been deleted, in which regions the heterologous DNA sequences are inserted (Levrero et al., Gene 101 (1991) 195; Gosh-Choudhury et al., Gene 50 (1986) 161). Other constructions contain a deletion in the E1 region and of a non-essential portion of the E4 region (WO 94/12649). These defective recombinant adenoviruses may be prepared in different ways, employing or otherwise a competent cell line capable of complementing all the defective functions essential for replication of the recombinant adenovirus. At the present time, the vectors derived from adenoviruses are generally produced in a complementation line (line 293) in which a portion of the adenovirus genome has been integrated. More specifically, line 293 contains the left-hand end (approximately 11-12%) of the adenovirus serotype 5 (Ad5) genome, comprising the left-hand ITR, the encapsidation region and the E1 region, including E1a, E1b and a portion of the region coding for the pIX protein. This line is capable of trans-complementing recombinant adenoviruses which are defective for the E1 region, that is to say lacking all or part of the E1 region, necessary for replication.

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L12: Entry 29 of 65 File: USPT Sep 28, 2004

DOCUMENT-IDENTIFIER: US 6797265 B2
TITLE: Deleted adenovirus vectors and methods of making and administering the same

Other Reference Publication (16):
Caravokyri et al.: Constitutive Episomal Expression of Polypeptide IX (pIX) in a 293-Based Cell Line Complement the Deficiency of pIX Mutant Adenovirus Type 5, Journal Of Virology 69:11 6627-6633 (1995).

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L12: Entry 36 of 65 File: USPT May 20, 2003

DOCUMENT-IDENTIFIER: US 6566128 B1
TITLE: Adenovirus vectors generated from helper viruses and helper-dependent vectors

Detailed Description Text (41):
The fourth embodiment of the invention, a cell line that supports the replication of the viral components of the invention, that expresses the Ad pIX, and that can be transfected with plasmids described in the previous examples has also been developed. Preferably, the cell line is a human cell line; however, other cell lines are also suitable such as Syrian hamster, mouse, bovine, porcine, or canine cells. These examples are not meant to be limiting as cells derived from other species are also suitable for use with the present invention. A 531 bp fragment of Ad5 DNA containing the pIX gene was placed under the regulation of an inducible metallothionein promoter or under the control of the human cytomegalovirus immediate early gene promoter and the Simian virus 40 polyadenylation sequence, transfected into 293 cells, and several clones that stably express pIX were identified (Krougliak and Graham 1995, Hum Gene Ther. 6:1575-1586). Cell lines VK2-20, VK4-24 and VK10-9 are capable of complementing a pIX-deficient Ad, and viral titers are similar to that of wild-type virus.

Other Reference Publication (35):
C. Caravokyri et al, "Constitutive Episomal Expression of Polypeptide IX (pIX) in a 293-Based Cell Line Complements the Deficiency of pIX Mutant Adenovirus Type 5". J. Of Virology, Nov. 1995, pp. 6627-6633.

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L12: Entry 56 of 65 File: USPT Sep 5, 2000

DOCUMENT-IDENTIFIER: US 6113913 A

** See image for Certificate of Correction **

TITLE: Recombinant adenovirus

Detailed Description Text (7):

The present invention provides a recombinant adenovirus having a genome with a deficiency in the E1 region and a mutation in the MLP. The deficiency in the E1 region is in region E1A, E1B, or both E1A and E1B, and recombinant viruses having such deficiencies are known in the art. Moreover, mutations of the E1 region can optionally affect the non-essential pIX gene. As is known in the art, deficiencies in the pIX gene reduce the packaging efficiency of large adenoviral genomes. Moreover, adenoviruses produced in the absence of the pIX gene product are more heat labile than wild-type adenoviruses. Despite these phenotypes, removal of a portion of the sequences governing pIX expression is preferred in some applications because such deficiencies minimize the sequence overlap between the adenoviral genome and the E1-complementing DNA of cell lines commonly used to propagate first-generation adenoviral vectors (e.g., HEK-293 cells), thus minimizing the likelihood that recombination events will generate an RCA. Preferably, the recombinant adenovirus of the present invention is at least deficient in a function provided by region E1 in combination with a deficiency in region E2 (i.e., E2A, E2B, or both E2A and E2B), and/or E3, and/or E4. More preferably, the recombinant adenovirus of the present invention comprises a deficiency in the E1 and E3 regions. While the adenovirus can have these, and other (e.g., one or more late regions (L1-L5)), deficiencies, to facilitate DNA replication and packaging of the recombinant genomes into maturing adenoviral capsids, preferably either at least the viral inverted terminal repeats and some of the promoters or at least the viral inverted terminal repeats and a packaging signal are left intact.

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L12: Entry 57 of 65 File: USPT Aug 1, 2000

DOCUMENT-IDENTIFIER: US 6096718 A
** See image for Certificate of Correction **
TITLE: Tissue specific adenovirus vectors for breast cancer treatment

Brief Summary Text (5):
For some applications, there may be a need to delete the E1 region, yet still preserve the replication capabilities of the adenovirus. For this purpose, the human embryonic kidney cell line 293 is suitable because E1 deleted adenoviruses will replicate in this cell line. This is because the host cells of 293 have been stably transfected with a DNA fragment containing the E1 and pIX genes, consequently are able to express proteins in a constitutive manner. Embryonic kidney cell line 293 provides proteins needed for viral replication after transfection of an E1 deleted adenoviral DNA, and allows the growing adenoviruses to enter a replicative program.

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L12: Entry 64 of 65 File: USPT Mar 16, 1999

DOCUMENT-IDENTIFIER: US 5882877 A
TITLE: Adenoviral vectors for gene therapy containing deletions in the adenoviral genome

Detailed Description Text (238):
The novel packaging system is based on the generation of an Ad protein pIX expressing 293 cell line. In addition, an adenoviral helper virus engineered such that the E1 region is deleted but enough exogenous material is inserted to equal or slightly exceed the full length 36 kb size. Both of these two constructs would be introduced into the 293/pIX cell line as purified DNA. In the presence of pIX, yields of both predicted progeny viruses as seen in current PAV/Ad2 production experiments can be obtained. Virus containing lysates from these cells can then be titered independently (for the marker gene activity specific to either vector) and used to infect standard 293 (lacking pIX) at a multiplicity of infection of 1 relative to PAV. Since research with this line as well as from incomplete or defective particle research indicates that full length genomes have a competitive packaging advantage, it is expected that infection with an MOI of 1 relative to PAV will necessarily equate to an effective MOI for helper of greater than 1. All cells will presumably contain both PAV (at least 1) and helper (greater than 1). Replication and viral capsid production in this cell should occur normally but only PAV genomes should be packaged. Harvesting these 93/pIX cultures is expected to yield essentially helper-free PAV.

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